

Tocilizumab in the treatment of patients with rheumatoid arthritis in real clinical practice: results of an Italian observational study

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Abstract

Objective

To describe the effectiveness and safety of tocilizumab (TCZ), an interleukin-6 receptor inhibitor, in a cohort of patients with rheumatoid arthritis (RA) recruited in clinical practice.

Methods

TRUST was an observational study in RA patients who started treatment with TCZ in the 6 months prior to site activation and were still on treatment at start of study; patients were followed up to 12 months after the first TCZ infusion.

Results

322 RA patients were enrolled in 59 Italian centres (mean age: 55.8 years; mean disease duration: 120.5 months; baseline DAS28: 5.3). After 6 months of TCZ treatment, patients achieving low disease activity (DAS28 \leq 3.2; 57.52%) or disease remission (DAS28 < 2.6; 38.05%) were 216 out of 226 patients with available DAS28 ($p < 0.001$).

No statistically significant differences were found in mean DAS28 and HAQ score changes from baseline (start of TCZ treatment) to study end between patients previously inadequately responding to disease-modifying anti-rheumatic drugs (DMARD-IR) or to DMARDs plus tumour necrosis factor inhibitors (DMARD + TNFi-IR): both patient populations responded to TCZ. A statistically significant decrease in mean VAS Fatigue score (48.4 vs. 34.7; $p = 0.0025$) at month 6 was observed. In patients treated with TCZ as monotherapy (32.61%), DAS28, VAS fatigue and HAQ scores decreased from baseline to any post-baseline time point. Overall, 62 patients (19.3%) prematurely discontinued TCZ treatment, 24 (7.5%) for safety reasons. Drug-related adverse events occurred in 92 patients (28.6%) (mostly 3 hypercholesterolaemia and leucopenia) and drug-related serious adverse events in 11 patients (3.4%).

Conclusion

This study confirms the good effectiveness and safety profile of TCZ in real life RA patient care.

Key words

tocilizumab, rheumatoid arthritis, interleukin-6, monotherapy

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Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disease affecting approximately 0.5–1% of the population worldwide, is characterised by chronic synovitis and progressive destruction of cartilage and bone in multiple joints, and is often associated with systemic manifestations such as anaemia, fatigue and osteoporosis (1).

The pathogenesis of RA is complex but dysregulation of inflammatory cytokines seems to play a pivotal role. Among these, interleukin-6 (IL-6), a pleiotropic pro-inflammatory cytokine produced by multiple cell types, may play a significant role (2). IL-6 exerts its effects through both membrane-bound (mIL-6R) and soluble (sIL-6R) IL-6 receptors. Elevated IL-6 levels are observed in serum and synovial fluid of RA patients and correlate with disease activity and radiological joint damage (3, 4). Many of the articular manifestations of RA could be explained by the biologic effects of IL-6: it can cause synovitis and joint destruction by stimulating neutrophil migration, inducing osteoclast differentiation and promoting pannus development as well as by increasing vascular endothelial growth factor (VEGF) expression (1). Moreover, IL-6 induces acute-phase protein synthesis, including C-reactive protein (CRP), through hepatocyte stimulation (5), and contributes to the systemic manifestations of RA: IL-6 stimulates the production of hepcidin, a liver peptide modulating hemoglobin production by restricting iron availability (6), playing an important role in the pathogenesis of anaemia; IL-6 can modulate the hypothalamic-pituitary-adrenal (HPA) axis, whose abnormality has been linked to the development of fatigue (7, 8), and acts on bone metabolism, with accelerated bone resorption and reduced bone formation (1), leading to osteoporosis. For the key role played by IL-6 in these RA manifestations, its blockade represents a useful therapeutic approach to RA treatment (1, 9, 10).

Tocilizumab (TCZ) is a humanised anti-IL-6 receptor (anti-IL-6R) monoclonal antibody, which inhibits IL-6 binding to both soluble and membrane-bound receptors, preventing IL-6-mediated pro-

inflammatory activity (11, 12). TCZ in combination with methotrexate (MTX) is indicated in patients with moderate to severe active RA, with inadequate clinical response (IR) or intolerance to disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor inhibitors (TNFi). Moreover, TCZ is indicated as monotherapy in patients intolerant to MTX or for whom MTX is considered inappropriate (13).

Several randomised clinical trials and long-term extension trials confirmed TCZ effectiveness and safety in RA treatment both as monotherapy and in combination with MTX (14–29).

Furthermore, observational studies have been performed to evaluate effectiveness, safety and usage patterns of TCZ in real clinical practice: all these studies confirmed the safety profile of TCZ and showed clear improvements in all recorded RA parameters (30–33). These real life data are of crucial importance, because the percentage of responding patients is usually lower in everyday clinical practice than that observed in randomised clinical trials, possibly because of patient selection, differences in doses, co-morbidities and adherence to therapy (34).

So far, very few Italian data on the use and clinical impact of TCZ in a real life setting are available (35). TRUST study was undertaken to collect data on the use of TCZ in real clinical practice in order to evaluate effectiveness, safety and routine usage pattern of TCZ in Italy.

Materials and methods

Patients

Patients aged ≥18 years, suffering from moderate to severe RA, according to the 1987 American College of Rheumatology (ACR) classification criteria (36), and starting TCZ treatment, in accordance with the Summary of Product Characteristics (SmPC) (37), in the 6 months prior to the study onset were enrolled. Patients were excluded if they had severe ongoing infections, hypersensitivity to the active substance or any of the excipients and if they were pregnant women.

Study protocol

TRUST was a national, multicentre, retrospective and prospective, non-in-

terventional study in RA patients treated with commercially available intravenous TCZ, performed in 59 Italian rheumatological centres. Patients starting TCZ treatment in normal clinical practice in the 6 months prior to site activation and still receiving treatment at the beginning of the study were included. All data of patients until the signature of informed consent were collected retrospectively and patients were then followed prospectively up to 12 months from the first infusion as presented in the explanatory figure of the study design (Fig. 1).

In accordance with the observational nature of the study, dosage and duration of TCZ treatment were decided by the physician, according to the approved product information, the local treatment guidelines and the daily medical practice: all procedures are consistent with normal clinical practice and no additional diagnostic or monitoring procedures which might modify the routine clinical practice have been applied to the patients. The approved dosage, according to the SmPC, is 8 mg/kg body weight, once every 4 weeks. The period of patient enrolment was 12 months. Any concomitant medication was recorded. No additional visits, clinical, instrumental or laboratory assessments were required outside of local routine clinical practice. When available, effectiveness and safety data were collected at baseline and 1, 2, 4, 6 and 12 months after the first TCZ infusion.

Clinical effectiveness was evaluated using 28-joint Disease Activity Score (DAS28), Visual Analogue Scale (VAS) Fatigue and Health Assessment Questionnaire (HAQ) as showed in the study flow-chart (Table I). Safety was assessed by examining the incidence of adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation and adverse events of special interest (AESI). The results of laboratory parameters (hematology, blood chemistry, serology, serum electrophoresis) were also recorded. Screening diagnostic tests performed at baseline included in all subjects tuberculosis skin test (PPD test) and Interferon Gamma Release Assays (IGRA).

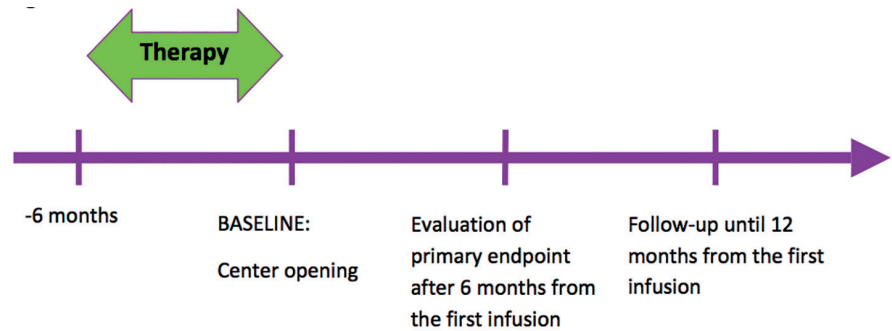


Fig. 1 Study design.

Study objectives

The primary objective of the study was to describe the percentage of RA patients treated with TCZ achieving low disease activity (DAS28 ≤ 3.2) or disease remission (DAS28 < 2.6) after 6 months of treatment. Secondary objectives included: comparison of TCZ effectiveness in real life between two different subpopulations, classified according to the previous pharmacological treatment: patients with inadequate response to disease-modifying antirheumatic drugs (DMARD-IR) or to DMARDs plus tumour necrosis factor inhibitors (DMARD + TNFi-IR); assessment of TCZ clinical benefits in patients treated as monotherapy (through evaluation of DAS28, VAS fatigue and HAQ scores); safety evaluation of TCZ treatment (standard adverse events, drug-related adverse events, serious adverse events and adverse events of special interest).

Ethics

The study protocol was approved by the local Independent Ethics Committee (IEC) of each participating centre. The study was conducted in full accordance with the principles of the Declaration of Helsinki and Italian laws and regulations. Written informed consent was obtained from each patient, before any study-related procedure was started.

Statistical analysis

The sample size was determined with reference to the final estimate of the proportion of RA patients achieving remission (DAS28 < 2.6) after 6 months of TCZ treatment. An expected value of 31.9% was calculated, resulting from the average of 30.1% reported by RA-

DIATE (28) and 33.6% by AMBITION study (15), and assuming a dosage of 8 mg/kg every 4 weeks for 6 months. The sample size turned out to be 236 patients, assuming to estimate this proportion by a one-side confidence interval (CI) 95% and choose as a distance from the lower limit a value of 5%. Considering a drop-out rate of 20%, the sample size was 295 patients, rounded up to 300 for convenience. Statistical analyses were performed using SAS System software (v. 9.2 or later) and were mainly descriptive. Continuous variables were summarised by descriptive statistics (number of cases, mean, standard deviation, median, minimum and maximum). Categorical variables were summarised using counts of subjects and percentages.

Adverse events were assigned a preferred term (PT) and categorised into System Organ Class (SOC), according to the Medical Dictionary for Regulatory Activities (MedDRA) classification, v. 14.1. Laboratory tests values were summarised using descriptive statistics.

Results

Patient demographics and baseline characteristics

Overall, 322 RA patients treated with TCZ were enrolled in 59 Italian rheumatological centres between May 2011 and April 2013: 260 patients (80.8%) completed the study, 62 patients (19.2%) withdrew prematurely. The reasons for premature withdrawal were: safety concerns (24 patients), insufficient therapeutic effect (17 patients), insufficient compliance (9 patients), remission of disease (2 patients), lost to follow-up (5 patients) and others (5 patients). Demographics and baseline

Table I. Study flow-chart.

Assessments/Procedures (available data were collected)	Visit 1 Baseline	Visit 2 Month 1 (as per clinical practice)	Visit 3 Month 2 (as per clinical practice)	Visit 4 Month 4 (as per clinical practice)	Visit 5 Month 6 (as per clinical practice)	Visit 6 Month 12 (as per clinical practice)
Written informed consent	X					
Check inclusion/ exclusion criteria	X					
Demographic data	X					
Diagnosis of RA (ACR criteria)	X					
Prior specific RA treatments (anti-TNF- α DMARDs, etc.)	X					
Specific history of RA at TCZ therapy start (lab and instrumental examinations)	X					
TCZ dose modification during therapy	X	X	X	X	X	X
DAS28	X	X	X	X	X	X
VAS Fatigue	X	X	X	X	X	X
Joint count	X	X	X	X	X	X
HAQ	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Co-morbidities	X	X	X	X	X	X
Ultrasound evaluation II° and III° MCP joint	X	X	X	X	X	X

disease characteristics of the study population are shown in Table II.

At baseline, 238 patients (73.91%) had one or more concurrent diseases. The most commonly reported diseases were hypertension (130 patients, 54.62%), muscular disorders (81 patients, 34.03%), metabolic disorders (57 patients, 23.95%) and endocrinological diseases (53 patients, 22.27%). PPD test was positive in 11 patients and IGRA test in 8 patients.

Before initiating TCZ treatment, most patients (319 out of 322) had been on treatment with a DMARD, associated with a TNFi in 231 patients. During the study, 319 patients (99.1%) took at least one concomitant treatment. Systemic corticosteroids (262 patients, 81.4%), methotrexate (186 patients, 57.8%), anti-ulcer drugs (182 patients, 56.5%) and non-steroidal anti-inflammatory drugs (156 patients, 48.4%) were the most frequently reported concomitant drugs.

Clinical effectiveness

• Primary end point

Available data on DAS28, VAS Fatigue and HAQ scores were collected at baseline and 1, 2, 4, 6 and 12 months after the first TCZ infusion. Patients starting treatment with TCZ but failing before 6 months were excluded from the analysis, according to the primary end point aimed at the evaluation of

Table II. Patients demographics and clinical characteristics at baseline.

Characteristics	n (%)
Age (years), mean \pm SD (n=322)	55.8 \pm 11.6
Gender (n=322)	
Female	260 (80.75)
Male	62 (19.25)
Weight (kg), mean \pm SD (n=322)	70.3 \pm 14.7
Height (cm), mean \pm SD (n=303)	163.4 \pm 7.9
BMI (kg/m ²), mean \pm SD (n=303)	26.3 \pm 5.3
Race (n=322)	
Caucasian	316 (98.14)
Black	2 (0.62)
Asian	2 (0.62)
Other	2 (0.62)
Disease duration (months), mean \pm SD (n=322)	120.5 \pm 94.9
SJC (out of 28), mean \pm SD (n=308)	5.8 \pm 5.2
TJC (out of 28), mean \pm SD (n=306)	9.8 \pm 6.7
DAS28, mean \pm SD (n=287)	5.3 \pm 1.2
VAS Fatigue, mean \pm SD (n=157)	59.8 \pm 24.1
HAQ, mean \pm SD (n=232)	1.5 \pm 0.7
Previous treatments (n=322)	
DMARD	319 (99.07)
TNFi	231 (71.74)
Other treatment for arthritis	276 (85.71)
Patients treated with TCZ as monotherapy (n=322)	105 (32.61)

SD: standard deviation; BMI: Body Mass Index; SJC: swollen joints count; TJC: tender joints count; DAS28: 28-joint Disease Activity Score; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying anti-rheumatic drug; TNF: tumour necrosis factor inhibitor; TCZ: tocilizumab.

the percentage of patients achieving DAS28 low disease activity or remission after 6 months of therapy. After 6 months of TCZ treatment, DAS28 data were available in 226 patients; the percentage of patients achieving low disease activity (DAS28 \leq 3.2)

(n=130, 57.52%, p -value=0.0237) or disease remission (DAS28 <2.6) (n=86, 38.05%, p -value=0.0003) was statistically significant (Table III). At the end of the study, the percentage of patients achieving low disease activity or disease remission rose to 70.4% and

53.2% respectively in the 186 patients with available DAS28 (Table III).

• Secondary end points

The results were analysed separately in patients with a previous inadequate response to DMARDs (DMARD-IR) or DMARD + TNFi-IR. Mean DAS28 and HAQ scores decreased from baseline to any post-baseline time point, without any statistically significant difference between the two groups, while statistically significant greater changes in mean VAS Fatigue score were observed among DMARD-IR patients (48.4 vs. 34.7, respectively; $p=0.0025$) after 6 months of treatment with TCZ (Fig. 2). A considerable proportion of patients (105 patients, 32.61%) were treated with TCZ as monotherapy: in these patients, mean DAS28, VAS Fatigue and HAQ scores decreased from baseline to any post-baseline time point (Fig. 3). These results suggest a downward trend for all these clinical parameters.

Safety

An overview of the safety results is shown in Table IV. Overall, 214 patients (66.5%) experienced at least one AE. The most common AEs were infections (111 patients, 34.5%). The infections (viral and bacterial) reported with a higher frequency were: bronchitis (24 patients, 7.5%); flu (16 patients, 5.0%); urinary tract infection (9 patients, 2.8%); rhinitis (7 patients, 2.2%); cystitis, pharyngitis, gastroenteritis, oral herpes, herpes zoster, nasopharyngitis (6 patients, 1.9% each). Other common AEs were: hypercholesterolaemia (23 patients, 7.1%), leucopenia (21 patients, 6.5%), neutropenia (17 patients, 5.3%) and elevations in liver transaminases (14 patients, 4.3%). Most of the adverse events were mild or moderate in intensity. A total of 92 patients (28.6%) experienced at least one drug-related adverse event (due to possible immune suppression). The most commonly reported drug-related AEs were hypercholesterolaemia (18 patients, 5.6%), leucopenia (15 patients, 4.7%), neutropenia (14 patients, 4.3%) and elevation in liver transaminases (9 patients, 2.8%). The increase in lipid levels was not associated with

Table III. Proportion of patients achieving low disease activity (DAS28 ≤ 3.2) or disease remission (DAS28 < 2.6), after 6 months of treatment with TCZ and at the end of the study.

	Month 6 (n=226)			End of study (n=186)		
	n	%	Lower limit Confidence interval 95%	n	%	Lower limit Confidence interval 95%
DAS28 ≤ 3.2 (low disease activity)	130	57.52*	52.11	131	70.43	63.87
DAS28 < 2.6 (disease remission)	86	38.05**	32.74	99	53.23	46.06

* $p=0.0237$; ** $p=0.0003$; DAS28: 28-joint Disease Activity Score.

clinical symptoms or major cardiovascular events.

Serious adverse events occurred in 28 patients (8.7%), with gastrointestinal perforation and pneumonia being the most frequently reported (2 patients each); the other SAEs occurred in one patient each. In 11 patients (3.4%), SAEs were considered to be drug related (due to possible immune suppression). All drug-related SAEs occurred in one patient each: bronchitis, pyelonephritis, tuberculosis, urosepsis, leucopenia, gynecomastia, abdominal pain, rectal hemorrhage, gastrointestinal perforation, dyspnea, interstitial lung disease, pneumonia and skin tumour excision. All the SAEs improved with appropriate treatment. No deaths were reported during the study.

AEs leading to treatment discontinuation occurred in 24 patients (7.5%). Those reported in more than one patient were: leucopenia (3 patients), neutropenia (3 patients), elevation in liver transaminases (2 patients) and gastrointestinal perforation (2 patients). Adverse events of special interest (AESI) were observed in 60 patients (18.6%): serious and/or medically significant infections in 44 patients (73.3%) (mostly pharyngitis, urinary tract infection, bronchitis, upper respiratory tract infection and rhinitis), serious and/or medically significant bleeding events in 7 patients (11.7%) (mostly epistaxis), serious and/or medically significant hepatic events in 5 patients (8.3%) (mostly elevation in liver transaminases), gastrointestinal perforations in 2 patients (3.3%) and malignancies in 2 patients (3.3%) (sigmoid colon and rectal cancer, and basal cell carcinoma excision). Pyrexia was the only drug-

related infusion reaction (reported in one patient), mild in intensity, but leading to withdrawal from the study.

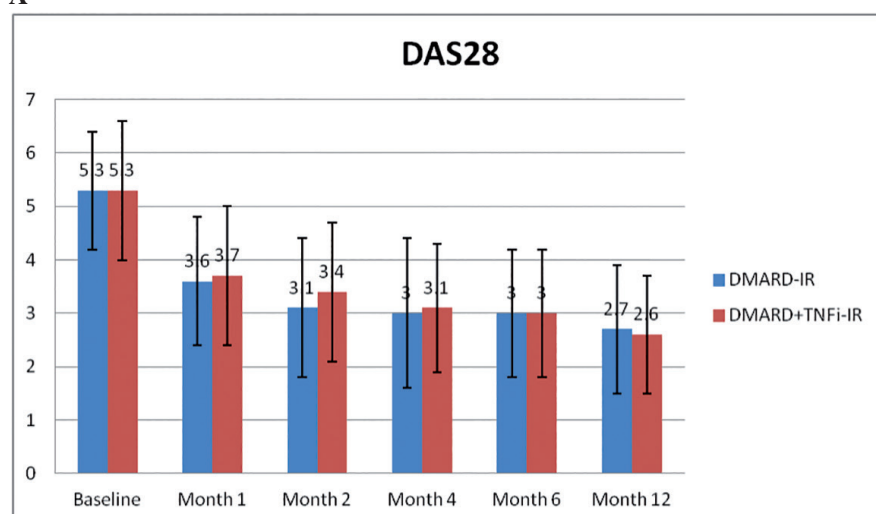
The changes in mean laboratory values from baseline to end of treatment included: an increase in hemoglobin levels (from 12.6 g/dL to 13.5 g/dL), a decrease in white blood cells (WBCs) (from 8,300 cells/ μ L to 6,300 cells/ μ L) and neutrophils (from 61.4% to 53.1%), an increase in alanine aminotransferase (ALT) (from 21.2 UI/L to 26.7 UI/L), aspartate aminotransferase (AST) (from 19.8 UI/L to 22.9 UI/L), total cholesterol (from 203.9 mg/dL to 214.4 mg/dL), LDL cholesterol (from 122.3 mg/dL to 126.3 mg/dL), HDL cholesterol (from 59.2 mg/dL to 62.4 mg/dL). The mean levels of the inflammation markers decreased markedly: erythrocyte sedimentation rate (ESR) from 37.4 mm/h to 8.9 mm/h and CRP from 21.7 mg/L to 3.9 mg/L (results not shown).

A marked decrease in anti-cyclic citrullinated peptide (ACPA) antibody, a decrease in median values of rheumatoid factor, in alpha-1, alpha-2, beta- and gamma-globulin, and an increase in albumin mean values were also observed (results not shown).

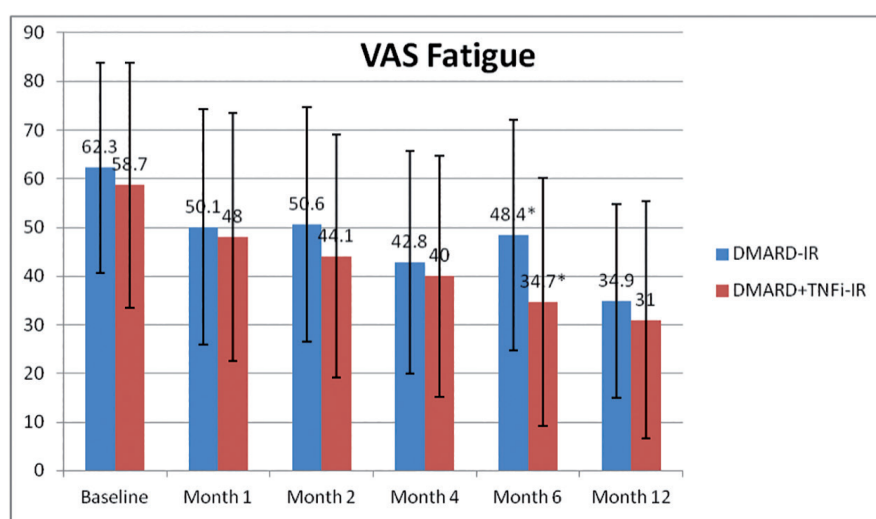
Discussion

This observational study performed in RA patients treated with TCZ was designed to collect data on the effectiveness, safety and routine use pattern of TCZ in real clinical practice in Italy. The effectiveness results were consistent with those reported in previous non-interventional studies (30-32). In the present study, over half of patients achieved low disease activity (DAS28 ≤ 3.2) and more than a third achieved disease remission (DAS28 < 2.6) after

A



B



C

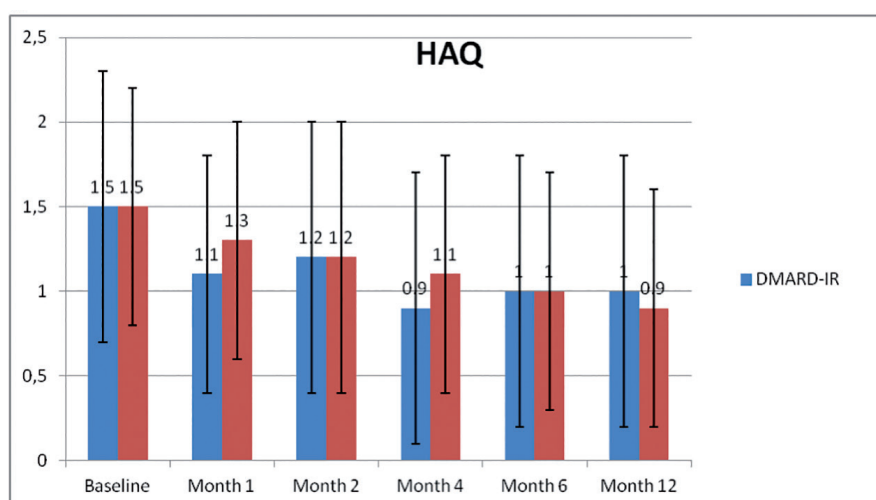


Fig. 2. Mean values of DAS28 (A), VAS Fatigue (B) and HAQ (C) scores in the DMARD-IR (n=89) and DMARD+TNFi-IR (n=230) subpopulations at each time point. * $p=0.0025$ (DMARD: disease-modifying anti-rheumatic drug; TNFi: tumour necrosis factor inhibitor; DAS28: 28-joint Disease Activity Score; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire).

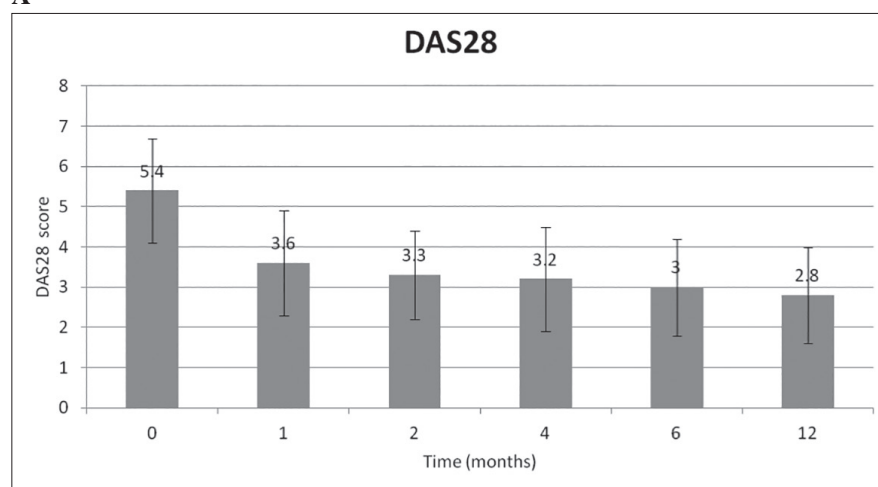
6 months of TCZ treatment, confirming the excellent effectiveness of TCZ. DAS28 scores continued to improve throughout the 12-month observation period, suggesting that clinical effectiveness is sustained and progressive over at least 12 months. The DAS28 score decrease was associated with improvements in patient global health, quality of life and daily living activity (as shown by decrease in HAQ and VAS Fatigue scores). The well-known effect of TCZ on systemic inflammation was also confirmed with evidence of a rapid, marked and sustained decrease in acute-phase response markers (CRP level and ESR).

A comparable effectiveness of TCZ treatment was observed between the two identified subpopulations, classified according to the previous pharmacological treatment, of patients DMARD-IR or DMARD + TNFi-IR, which indicates that the treatment response rate to TCZ is very good also in patients resistant to TNFi therapy even in real life scenarios.

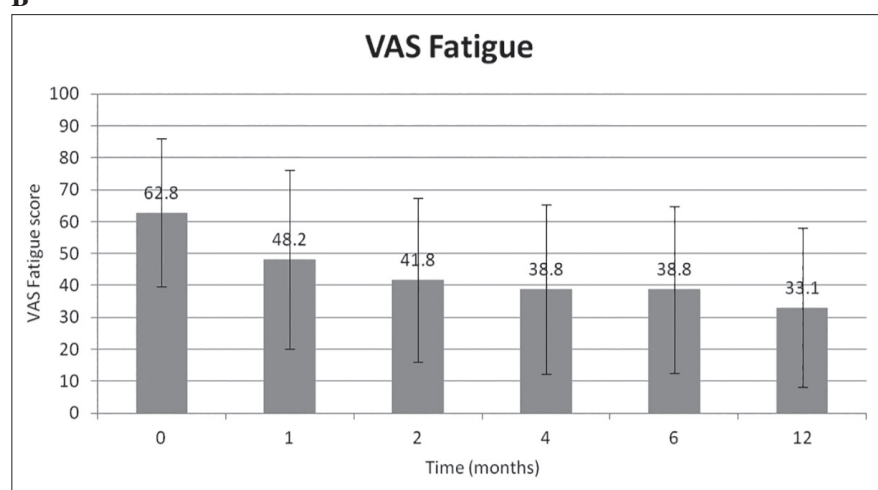
In this study, a considerable proportion of patients were treated with TCZ as monotherapy: all clinical parameters evaluated (DAS28, VAS Fatigue, HAQ) in these patients improved from baseline, suggesting a good clinical effectiveness of TCZ in this setting too. The high percentage of patients treated with monotherapy is similar to that reported in some European registries (30-32), confirming that TCZ is often prescribed as monotherapy in real clinical practice and is more often prescribed in MTX intolerant patients. Interestingly, over three fourth of patients were still taking systemic corticosteroids as concomitant drug after about 10 years of disease.

The safety results were consistent with the known safety profile of TCZ. The incidence and pattern of adverse events did not show new safety concerns or unexpected findings. Treatment with TCZ was generally well tolerated, with a low incidence of withdrawals due to safety issues; approximately two thirds of patients experienced adverse events during TCZ treatment, mostly mild or moderate in intensity: these AEs were judged to be treatment-related in just above one fourth of patients.

A



B



C

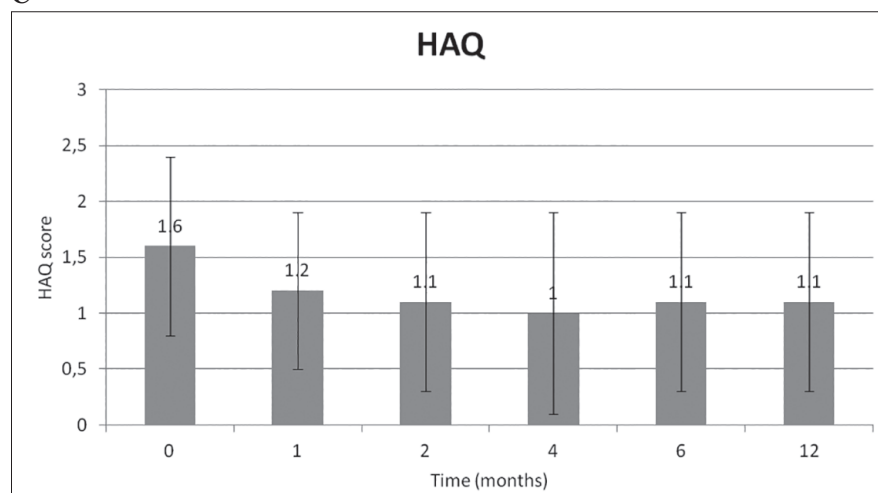


Fig. 3. Mean values of DAS28 (A), VAS Fatigue (B) and HAQ (C) scores at each time point in patients treated with TCZ as monotherapy (n=105). (DAS28: 28-joint Disease Activity Score; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire).

As observed in previous studies (15, 21, 25, 30, 31), the most commonly reported AEs were infections, mostly mild and leading to premature withdrawal only in

4 patients; an increased incidence of infections has also been observed with other monoclonal antibodies targeting the components of the immune system (38).

Table IV. Summary of safety data.

	n (%)
Any adverse event	214 (66.5)
Drug-related adverse events	92 (28.6)
Serious adverse events	28 (8.7)
Drug-related serious adverse events	11 (3.4)
Adverse events leading to treatment discontinuation	24 (7.5)
Adverse events of special interest	60 (18.6)
Deaths	0
Adverse events occurring in $\geq 5\%$ of patients	
Bronchitis	24 (7.5)
Hypercholesterolaemia	23 (7.1)
Leucopenia	21 (6.5)
Neutropenia	17 (5.3)
Flu	16 (5.0)
Serious adverse events occurring in ≥ 2 patients	
Gastrointestinal perforation	2 (0.6)
Pneumonia	2 (0.6)

Values are the number (%) of patients.

The most frequent AEs considered related to TCZ treatment were abnormal laboratory values: hypercholesterolaemia, leucopenia, neutropenia and elevation in liver transaminases.

These laboratory findings were on line with the known safety profile of TCZ. The increase in lipid levels was mostly mild and not associated with clinical symptoms or major cardiovascular events. As IL-6 is thought to play a causative role in atherosclerosis, IL-6 blockade may decrease the incidence of cardiovascular events (39); several studies have provided evidence that, despite increases in lipid levels, reduced inflammation markers have been associated with reduced cardiovascular events (40, 41). Mean WBCs and neutrophil counts decreased, but remained within the normal range. Although leucopenia and neutropenia were considered mild in most patients, 3 patients prematurely withdrew owing to leucopenia and 3 patients due to neutropenia. Some possible mechanisms by which TCZ may lead to lower neutrophil count include blocking IL-6-induced neutrophil survival and the margination of neutrophils from the circulation into tissues (28).

Liver transaminases (AST, ALT) increased slightly, but remained roughly within the normal range, as seen in previous studies (15-21). Although no clinical signs or symptoms of hepatitis or serious liver disorders were reported,

2 patients discontinued treatment due to elevation in serum transaminases. In conclusion, TCZ, the only up to date available drug targeting IL-6, represents a good therapeutic approach in RA patients. The study presents some limitations concerning his observational nature that could imply the analysis of non-homogeneous populations based on the open, non-randomised design of the study and regarding the high rate of missing data, above all in the retrospective part of the study data collection, due to the lack of a fixed visit schedule, according to the daily clinical practice. Moreover some comparison data between the two sub-populations of DMARD-IR and DMARD+TNFi-IR patients and between the TCZ mono and TCZ+DMARDs groups are not available. Our study in real life RA patients, confirms the effectiveness of TCZ, as shown by the high proportion of patients achieving low disease activity or disease remission. Furthermore, TCZ treatment showed a comparable effectiveness in patients DMARD-IR and DMARD+TNFi-IR. The clinical benefits of TCZ were also shown in patients treated as monotherapy, where all the considered clinical parameters improved. The low incidence of drug-related AEs and SAEs is consistent with the known safety profile of TCZ.

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